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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,464	03/28/2001	Martin Friede	B45070-1	1150

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,464	FRIEDE ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *1-46 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47, 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/2001, 01/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group V in the paper filed December 23, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-46, and 49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse (as indicated above) in the paper filed on December 23, 2003.

3. Currently, claims 47 and 48 are pending and under consideration in the application.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on March 26, 2001 and January 29, 2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

5. It is noted that the Lipford reference cited in the January 2004 IDS was also cited in the March 2001 disclosure. The later citation has therefore been crossed out as redundant.

Priority

6. Applicant's submission of a petition for a delayed claim of priority on January 13, 2004 is noted and a copy of the United Kingdom priority application GB 9513107.4. The Office has not yet made a determination as to the Applicant's petition.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 47 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on methods of stabilizing or reducing the reactogenicity of the saponin QS-21 by adding an "excess of sterol to the adjuvant formulation."

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). In the specification, the Applicant has indicated that such an excess "will typically be in the order of 1:100 to 1:1 weight to weight." App. page 5, lines 30-33. Thus, the Applicant appears to consider a ration of 1:1 saponin: sterol as being an excess of sterol, even the amounts of the two compounds may be equal.

However, in the art, it is generally understood that to have one compound in excess of another is the mean that the amount of the first compound exceeds or is greater than the other. See e.g., "excess" CancerWEB Online Medical Dictionary (cancerweb.ncl.ac.uk/omd/), and Stedman's Medical Dictionary, 27th Edition (www.stedmans.com). The term "excess" is therefore because the specification does not clearly redefine the term, and because the term is not generally understood to include an equal amount as being an excess.

9. Claims 47 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. As indicated above, the claims read on a method comprising the addition to a QS21 containing adjuvant formulation an excess of a sterol. In particular, the claims read that the methods include the "addition of excess sterol to the adjuvant formulation (weight/weight)." The claim language is indefinite for two reasons.

First, the claim describes the addition of an excess of sterol, then further, in parenthesis, makes the notation weight/weight. It is unclear from this language if the parenthetical notation is intended as a claim limitation (i.e. that the determination of whether an excess of sterol has been added may only be determined based on weight), or is merely an example of the means by which one of ordinary skill in the art could measure whether an excess of sterol has been added to the formulation.

Second, the claim language is also indefinite because it is not clear from the claims if the excess of sterol is an excess over the entire weight of the formulation to which it is added, or if the weight of the sterol need only be an excess over the weight of QS21.

Clarification is required.

Unless otherwise stated, for the purposes of this action it is assumed that the Applicant intended to claim methods wherein an excess by weight of sterol as compared to QS21 is added to the adjuvant formulation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 47 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by the teachings of Lipford et al. (Vaccine 12(1): 72-80, of record in the March 2001 IDS) in light of the teachings of Kensil et al., U.S. Patent 5,583,112. The claims have been described above. Lipford teaches the making of an immunogenic composition comprising 5mg of cholesterol and .4mg of Quil A. Thus, the reference teaches a method of combining an excess of cholesterol to saponin formulation. The saponin adjuvant used in the reference is Quil A, which is known in the art to be a crude extract of the Quillaja Saponaria Molina bark, and to comprise several saponins within it. See, Kensil, columns 12-13. Among the saponins within Quil A is QS-21. Id, and col. 3, lines 56-59. Thus, the Lipford reference teaches the use of an excess of cholesterol both to Quil A, and to QS-21. Because the method used in the reference comprises the limitations of the rejected claims, and because the formulations that are described in the reference appear to fall

within the scope of those use in the claimed method, it appears that Lipford performs the claimed method, and would also inherently achieve the results required by the claims.

12. Claims 47 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Mackenzie et al. (EP 0415794) in light of the teachings of Kensil (supra). The claims have been described above. This reference teaches an antigenic complex comprising the saponin adjuvant Quil A, and cholesterol in a preferred weight to weight ratio of 5:1 (respectively). Page 3, lines 43-47. The reference does not teach that the sterol is in excess of the Quil A.

However, as indicated above, Kensil teaches that Quil A comprises multiple saponins, including QS21. Kensil also teaches the relative proportions that each of the 23 identified saponins constitutes of Quil A. See, Table 1, column 13. In this table, Kensil indicates that QS21 constitutes only about 3.7 percent of the Quil A composition. The ration of 5:1 Quil A: sterol used in Mackenzie therefore appears to be a ration of about 0.185:1 of QS21:sterol. Thus, while the amount of sterol used by Mackenzie is not in excess of the Quil A composition, it is in excess of the QS21. The reference therefore teaches a method of adding to a QS21 adjuvant formulation an excess of sterol by weight in comparison to QS21.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 47 and 48 rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford in view of the teachings of Kensil. These claims have been described above. As indicated above, the Applicant has defined the term "an excess" such that a weight to weight ratio of 1:1 of QS21:sterol falls within its meaning for the purposes of this application. See, page 5, lines 29-35. Thus, the claims appear to read on methods of reducing the reactogenicity of QS-21 by adding sufficient cholesterol for a 1:1 weight to weight ratio. The teachings of Lipford and Kensil have been described above. Lipford teaches the making of a liposome comprising Quil A and an excess of cholesterol. Kensil teaches that QS-21 is component of Quil A with adjuvant properties comparable to or greater than Quil A. Thus, it would have been obvious to those in the art to substitute QS-21 for Quil A in the complex described by Lipford. Because the making of such a complex involves the addition of an excess of sterol to a saponin, the making of the suggested complex would inherently result in reducing the reactogenicity and hydrolysis of QS-21.

Conclusion

15. No claims are allowed.

16. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Morein et al., Clinical Immunotherapeutics, 3(6) : 461-75. This reference teaches the structure and components of adjuvant iscoms. In particular, the reference teaches that the critical components are Quil A, or selected Quillaja components, and cholesterol. Pages 464-65. Further, the reference teaches that free saponin components, while immuno-enhancing, also have toxic effects (reactogenicity). Page 466. The reference teaches that incorporation of these saponins into matrices (described as comprising the saponin and cholesterol) reduces the reactogenicity.

Boon et al., WO 98/57659. this reference teaches the addition of an excess of sterol to increase the stability and reduce the reactogenicity of QS-21 adjuvants. See, page 3 lines 24-30, and page 6 lines 4-8. However, these teachings are not considered prior art to the present application in view of the priority to PCT/EP96/01464.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel 3/22/04

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